

Increased Risk of Proteinuria among a Cohort of Lead-Exposed Pregnant Women

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Reports of renal dysfunction after exposure to lead have appeared in the literature for over a century (1,2). Excesses in mortality due to nephritis (3,4) and chronic hypertension (not associated with cardiovascular causes) (5) and renal diseases (6–10) have been observed among young adults surviving an epidemic of childhood lead encephalopathy in Australia and in workers in lead industries, respectively. Reductions in glomerular filtration rate (GFR) (11,12), creatinine clearance (13), and glucose transport (14) have been reported in adults with prolonged occupational exposure to lead. Together, these observations suggest that long-term, high-dose lead exposure is associated with increased mortality and morbidity due to renal dysfunction. Less is known, however, about the effect of more moderate environmental lead exposure on renal function. Exposure at environmental levels has been associated with small increases in both systolic and diastolic blood pressure (15–18) and with slight but statistically significant decreases in creatinine clearance (19).

During a prospective study of environmental lead and pregnancy outcome (20–22) in Kosovo, Yugoslavia, we measured proteinuria in lead-exposed pregnant women and a similar, but relatively unexposed, cohort. Leakage of protein into the urine may reflect functional and morphological changes in the kidney, findings associated with lead exposure in both animal and human models (23,24). Although a small amount of protein is normally present

in the urine of healthy, nonpregnant persons, the physiologic changes of pregnancy normally increase this amount (25–27). This study explored whether environmental lead exposure is associated with an increased rate of proteinuria during pregnancy.

Kosovska Mitrovica (K. Mitrovica), the site of a lead smelter, refinery, and battery plant, is a lead-exposed area (28). Pristina, a town 25 miles to the south, has minimal lead exposure. Between May 1985 and December 1986, 1502 women, at approximately 12–20 weeks of gestation and making their first prenatal visit, were recruited for a study of pregnancy outcomes. The final sample sizes were 900 women in Pristina and 602 women in K. Mitrovica. *A priori*, we excluded women who reported at least one of the following conditions: previous history of hypertension ($N = 22$), previous history of gestational hypertension ($N = 19$), and use of antihypertensive medication ($N = 6$). The mean blood lead concentration (BPb) for the 37 excluded women did not differ from that of the women included; however, their average systolic and diastolic blood pressures were slightly higher.

Subjects were interviewed by trained, bilingual (Serbo-Croatian and Albanian) nurses, who were not privy to the hypotheses concerning renal function. Women were similar with respect to age, education, parity, and ethnicity, with more than 50% of the sample of Albanian origin (Table 1). Gestational age at entry to study was earlier in K. Mitrovica than in Pristina (17 versus 19 weeks, respectively). Cigarette smoking

Long-term exposure to high concentrations of lead results in renal dysfunction. During a prospective study of environmental lead and pregnancy outcomes in 1502 women residing in two towns in Yugoslavia, we explored whether moderate exposure to lead results in increased rates of proteinuria. The geometric mean blood lead concentrations (BPb) were 17.1 and 5.1 $\mu\text{g/dl}$ in the smelter and nonexposed towns, respectively. Increases in BPb were associated with increased odds ratios for both trace and $\geq 1+$ proteinuria, measured using a urinary dipstick. Comparing the women in the upper 10th percentile of exposure to those in the lowest 10th percentile, the adjusted odds ratio for $\geq 1+$ proteinuria was 4.5 (95% CI 1.5, 13.6). Similarly, the adjusted odds ratio for trace proteinuria was 2.3 (95% CI 1.3, 4.1). Similar to other studies showing associations between chronic exposure to lead and renal dysfunction, our data suggest that long-term exposure to environmental lead may be associated with proteinuria. **Key words:** epidemiology, lead exposure, pregnancy, proteinuria. *Environ Health Perspect* 101:418–421(1993)

and alcohol use were reported more often in Pristina. More women were employed in Pristina.

A urine sample was obtained for dipstick analyses (Bili-Labstix, Ames, Miles Laboratories, Elkhart, Indiana) of protein. Dipstick analyses represent a qualitative assessment of protein in the urine. In the presence of protein, the reagent on the dipstick changes color; the color shade is proportional to the concentration of protein. Of the 1465 eligible women, 1447 (98.8%) provided urine samples. Proteinuria was trichotomized

Table 2. Distribution of midpregnancy dipstick proteinuria by town and in the total sample

	K. Mitrovica		Pristina		Total	
	N	%	N	%	N	%
Proteinuria ^a						
Negative	94	16.2	280	32.4	374	25.9
Trace	431	74.1	524	60.6	955	66.0
1+	55	9.4	48	5.6	103	7.1
2+	2	0.3	9	1.0	11	0.8
3+	0	—	3	0.4	3	0.2
4+	0	—	1	0.1	1	—

^aProteinuria levels on dipstick defined as follows: trace, <30 mg/dl; 1+, 30–100 mg/dl; 2+, 100–300 mg/dl; 3+, 300–2000 mg/dl; 4+, >2000 mg/dl.

Table 1. Demographic characteristics of the study population at midpregnancy

Variable	K. Mitrovica (N=587)	Pristina (N=878)	p^a
Maternal age (years)	26.3 (5.2) ^b	26.9 (4.9)	0.0363
Maternal education (years)	8.9 (4.2)	9.1 (4.1)	0.5524
No. of previous pregnancies	2.1 (2.2)	2.3 (2.3)	0.0694
Maternal ethnicity			
% Albanian	55.8	60.8	0.041
% Serbian	25.4	25.1	
% Other	18.8	14.1	
Gestation at interview (days) ^c	118.5 (26.1)	131.3 (29.7)	0.0001
% Cigarette smokers ^d	24.9	28.2	0.157
% Alcohol users ^d	5.1	9.6	0.002
% Mothers employed	33.0	45.4	0.0001
% Mothers working during pregnancy ^e	76.7	76.1	

^aContinuous variables assessed by *t*-test; categorical variables assessed by chi-square statistic.

^bData are means; SD in parentheses.

^cCalculated as days from last menstrual period.

^dPercent includes level of any use.

^eOf those women employed.

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Table 3. Hematologic parameters at midpregnancy^a

Measure	K. Mitrovica (N = 587)	Pristina (N = 878)	<i>p</i> ^b
BPb (μg/dl)	17.1 (16.5,17.8)	5.1 (5.0,5.3)	0.0001
EP (μg/dl)	35.8 (34.0,37.8)	25.2 (24.4,25.9)	0.0001
SF (μg/ml)	14.2 (13.1,15.4)	11.7 (10.9,12.5)	0.0049
Hb (g/dl)	12.4 (12.3,12.5)	12.3 (12.2,12.4)	0.1103

^aData for blood level (BPb), erythrocyte protoporphyrin (EP) and serum ferritin (SF) are geometric means; 95% CIs in parentheses. Geometric means were calculated as $1/n[\log_{10}(x_1) + \log_{10}(x_2) + \dots + \log_{10}(x_n)]$. Data for hemoglobin (Hb) are expressed as arithmetic means.

^bStatistical significance by *t*-test.

as none, trace, and $\geq 1+$, representing a modification of the recommendations of the Committee of Terminology of the American College of Obstetricians and Gynecologists (29,30).

The overall high prevalence of proteinuria (72%; Table 2) in this study may be attributed to normal physiological changes in renal function during pregnancy (25). GFR increases early in pregnancy and remains elevated until the month before delivery (26,27). These changes result in increased urinary excretion of glucose, amino acids, water-soluble vitamins, and protein. Trace proteinuria was detected in 89% of all women with proteinuria. Very few women had levels of 2+ or greater (i.e., levels that might indicate a clinically significant renal disorder).

Venous blood samples were obtained for the measurement of BPb (31), erythrocyte protoporphyrin (EP) (32), serum ferritin, (33), and hemoglobin. Blood specimens were refrigerated until transported to Columbia University, where the laboratory participates in the Centers for Disease Control BPb and EP quality control program and is certified for BPb analyses by the Occupational Safety and Health Administration. During the course of the study period, agreements with the CDC values for BPb and EP, measured by intraclass correlation coefficients, were 0.95 and 0.99, respectively.

Both BPb and EP were substantially higher in K. Mitrovica (geometric means of 17.1 μg/dl and 35.8 μg/dl, respectively) than in Pristina (geometric means of 5.1 μg/dl and 25.2 μg/dl, respectively; Table 3). The ranges of BPb were 3.0–56.7 μg/dl in K. Mitrovica and 1.3–23.0 μg/dl in Pristina.

We used logistic regression analyses (34,35) to estimate the association between lead and proteinuria, adjusting for potentially confounding variables (see Table 4). These variables were associated with proteinuria ($p < 0.25$) or changed the coefficient of the exposure variable by more than 10% when included in the model. Data on acetaminophen use, a predictor of proteinuria, began to be collected midway through the study and was obtained only on a subset of women ($N = 425$). We examined these women separately and found essentially similar associations between lead and proteinuria.

Blood lead levels represented recent exposure. We first ranked the BPb levels of individual women from highest to lowest and divided them into exposure deciles. The estimated adjusted odds ratios for both trace and $\geq 1+$ proteinuria appeared to increase in the highest exposure deciles. For $\geq 1+$ proteinuria (Fig. 1), the increase appeared when BPb was greater than approximately 5.8 μg/dl; the estimated adjusted odds ratios (95% CI) above this value ranged from 2.1 (0.8, 6.4) to 8.4 (2.7, 26.5). For trace proteinuria (Fig. 2), the increases appeared when BPb was greater than approximately 6.7 μg/dl, after which the estimated adjusted odds ratios showed a monotonic increase ranging from 1.6 (1.0, 2.7) to 3.4 (1.8, 6.3).

Blood lead was then considered as a continuous variable. We report results for the logarithmic transformation of BPb; results for the untransformed metameter were essentially the same. For $\geq 1+$ proteinuria, the estimated adjusted log odds was 1.8 (95% CI 1.0, 2.5) per log unit increase in BPb. Although lower than in the combined data, the log odds in K. Mitrovica

and Pristina (Table 4) did not statistically differ from each other ($p = 0.72$). For trace proteinuria, the estimated adjusted log odds was 1.2 (95% CI 0.8, 1.6) per log unit increase in BPb. The log odds in K. Mitrovica (0.95) was above the null value and slightly, but not significantly, differed from that in Pristina (−0.2; $p = 0.13$).

We estimated cumulative exposure based on zone of residence and duration at that location. Zones were defined by a series of concentric circles around the smelter with radii progressively increasing by 2 km; thus, zone 1 was defined as the area within 2 km of the smelter, zone 2 as the area between 2 and 4 km from the smelter, etc. Zone 5 was the area between 8 km from K. Mitrovica and Pristina. Zone accounted for the largest proportion of the variance in midpregnancy BPb (20).

Neither trace nor $\geq 1+$ proteinuria was associated with zone and duration of residence. Comparing zones 1–4 to zone 5, the estimated odds ratios for $\geq 1+$ proteinuria were 0.7, 1.2, 1.0, and 0.2, respectively. Comparing zones 1–4 to zone 5, the estimated odds ratios for trace proteinuria were 1.1, 1.1, 1.2, and 1.7, respectively. Each of these odds ratios had wide 95% CI, which were consistent with the null value of 1.0.

These analyses suggest slight elevations in the risk of both trace and $\geq 1+$ proteinuria at midpregnancy after exposure to environmental lead. Most of the exposed women lived in the smelter area for long periods of time, and exposure was probably higher earlier in life (28). In a subset of women from this study, we previously reported reduced serum erythropoietin (a renal hormone) among pregnant women with the highest BPb levels (36). Staessen et al. (19), in a sample of men and women from four areas in Belgium, found an inverse association between BPb and creatinine clearance, indicating a reduction in GFR after exposure to lead. Collectively, these observations suggest adverse renal effects of lead at more moderate exposures than those previously reported in the occupational literature.

The present analyses also suggest a threshold effect for trace proteinuria. The estimated log odds for BPb was elevated only in K. Mitrovica, where exposure levels are relatively high, suggesting that the BPb levels in Pristina may be below the non-observable effect level. Although the log odds in K. Mitrovica was not statistically significant, post hoc calculations revealed relatively low power (about 40%) for this outcome. Moreover, results from the grouped BPb suggested elevations in the odds ratio for trace proteinuria when BPb exceeded 6.4 μg/dl. Alternatively, however, both the narrow range of exposure in

Table 4. Estimated adjusted log odds of blood lead (BPb; log μg/dl) on $\geq 1+$ and trace proteinuria at midpregnancy

	Both towns		Pristina		K. Mitrovica	
	Log odds	95% CI	Log odds	95% CI	Log odds	95% CI
$\geq 1+$ ^a	1.78	1.00,2.55	1.31	-0.49,3.12	0.74	-0.91,2.40
Trace ^b	1.20	0.78,1.62	-0.19	-1.10,0.73	0.95	-0.16,2.06

^aControlling for cigarette smoking (yes, no), height (linear and quadratic), age (linear and quadratic), average daily consumption of milk (glasses/day), gestational age (linear and quadratic), number of previous live births, average weekly consumption of meat (times/week), and hemoglobin.

^bControlling for cigarette smoking (yes, no), ethnic group (Albanian, Serbian, other), age, average weekly consumption of meat (times per week), average daily consumption of milk (glasses per day), and hemoglobin.

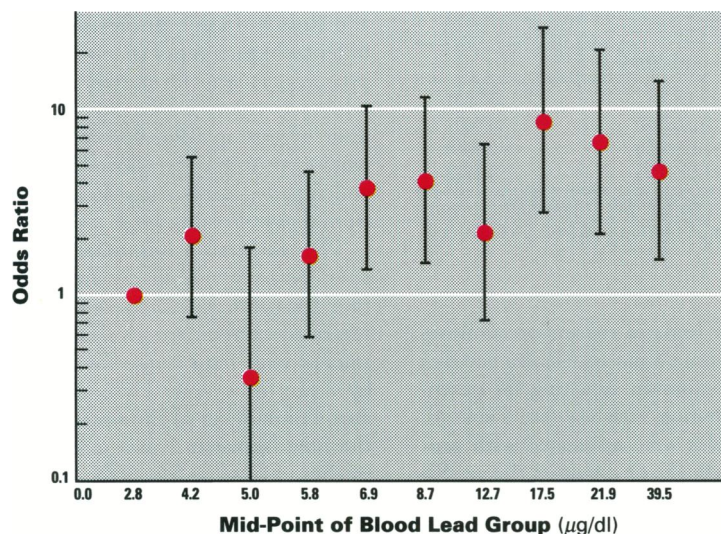


Figure 1. Adjusted odds ratios (bars indicate 95% CIs) for $\geq 1+$ proteinuria. Blood lead groups were defined by ranking BPb levels in ascending order and defining 10 groups with approximately equal numbers in each. Group 1 is always used as the reference. The odds ratios are adjusted for cigarette smoking (yes, no), height (linear and quadratic), age (linear and quadratic), average daily consumption of milk (glasses/day), gestational age (linear and quadratic), number of previous live births, average weekly consumption of meat (times/week), and hemoglobin.

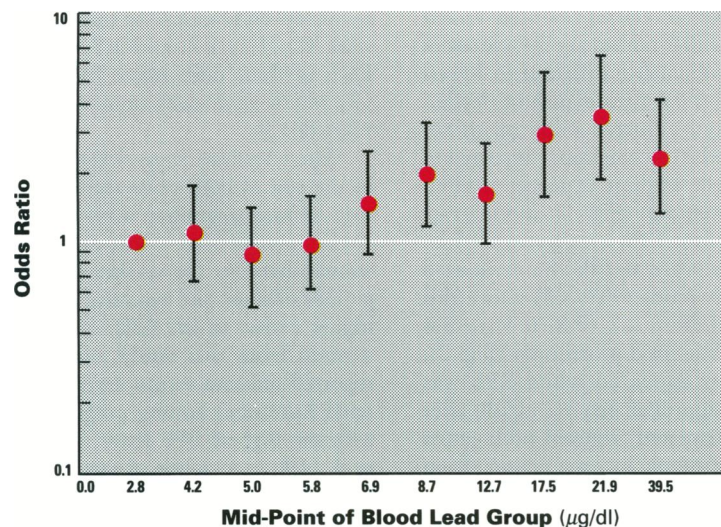


Figure 2. Adjusted odds ratios (bars indicate 95% CIs) for trace proteinuria. Blood lead groups were defined by ranking BPb levels in ascending order and defining 10 groups with approximately equal numbers in each. Group 1 is always used as the reference. The odds ratios are adjusted for cigarette smoking (yes, no), ethnic group (Albanian, Serbian, other), age, average weekly consumption of meat (times per week), average daily consumption of milk (glasses per day), and hemoglobin.

Pristina and the high overall prevalence of proteinuria may have obscured the result.

Similarly, results of the grouped BPb analysis did show statistically significant elevations in the odds ratio for $\geq 1+$ proteinuria when BPb exceeded 5.3 $\mu\text{g}/\text{dl}$. Nevertheless, when BPb was considered as a continuous variable, the log odds in K. Mitrovica, although suggestive of an association, was not statistically significant. Again, relatively low post hoc power (about 14%) was found to detect the observed log odds. Our failure to find statistically significant results in the analyses

of BPb as a continuous variable may thus be attributed to inadequate sample size and/or incorrect specification of the shape of the curve. Although we cannot exclude the null result, neither can we exclude an association between BPb and proteinuria.

For both $\geq 1+$ and trace proteinuria, the log odds for the combined data are higher than for each town separately, suggesting an effect of town. Cadmium, emitted from the smelter at far lower concentrations than lead (37), is known to adversely affect renal function. We have previously demonstrated that placental cadmium concen-

trations in a subset of these women are 1000 times lower than placental lead (37). Nevertheless, studies in animals and in populations with high exposure to cadmium (38) suggest that cadmium affects both glomerular and tubular function, resulting in proteinuria, glucosuria, amino aciduria, and disorders involving impaired tubular resorption. In a population in Belgium, increased urinary cadmium excretion has been associated with a variety of markers of proximal tubule damage (39), including urinary retinol-binding protein and *N*-acetyl- β -glucosaminidase. Thus, because trace quantities are emitted from the smelter in K. Mitrovica, cadmium cannot be excluded as a contributory factor.

We were unable to determine the mechanism of the proteinuria because urine dipsticks cannot assign protein molecular weight. Low-molecular-weight proteinuria would indicate damage to the proximal renal tubules, associated with the early stages of lead nephropathy, whereas proteinuria consisting of high-molecular-weight molecules would indicate increased glomerular permeability, indicative of later-stage lead nephropathy (23,24). Urinary dipsticks have been shown to be more sensitive to albumin than to other proteins (40,41) but are not specific to albumin. In conclusion, this study supports the hypothesis that lead exposure is associated with subclinical renal dysfunction during pregnancy.

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